Review Article

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Fatty liver – current look at the old disease

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SUMMARY

The report is devoted to the presentation of aetiological factors causing fatty liver, including alcohol, obesity, diabetes mellitus, hyperlipoproteinaemias and drugs. The author discusses morphological changes typical for the fatty liver such as large or small fatty droplets in hepatocytes and rarely coexisting hepatitis (so-called steatohepatitis). The work presents symptoms, changes in biochemical analyses of serum as well as methods of the liver visualisation used in the diagnostics of fatty liver. The treatment in based on the elimination of aetiological factors and properly balanced diet with support of pharmacotherapy in selected cases.

Fatty liver (steatosis; FL) is defined when fat, mainly triglycerides (TG), exceeds 5% of the liver weight [1]. According to the other description, it is an accumulation of fat droplets in over half of hepatocytes. FL is a morphological description of the status of the liver parenchyma and it represents the organ response to different noxious factors. Normal liver contains small fat droplets in hepatocytes, however they are seen only in the electron microscopic studies.

Etiopathogenesis. The factors responsible for the development of disturbances in lipid metabolism of the liver are presented in Table 1. Pathomechanism of FL is still not fully discovered.

The liver plays a central role in the lipid metabolism. It takes up free fatty acids (FFA) derived from the chylomicrons which transport dietary fat absorbed from the intestine and FFA liberated from adipose tissue. A part of FFA is oxidised to CO2 or ketone bodies in the hepatocyte mitochondria and the majority is incorporated in composed lipids, i.e. TG, phospholipids and cholesterol esters [1–4]. FFA are also synthesised de novo in the hepatocyte [1,4,5]. TG packed with apoproteins, phospholipids and cholesterol are exported from liver cell as very low density lipoproteins (VLDL; [1,4,5]). Lipoproteins are synthesised and degraded in the liver and chylomicrons; low density lipoproteins (LDL) and high density lipoproteins (HDL) are catabolised in hepatocytes as well [1,2,4,5].

Theoretically, FL could accumulate through at least four mechanisms:

1. increased delivery of dietary fat absorbed from the small intestine. Fat incorporated into chylomicrons enters the circulation and is transported to the liver. Moreover, FFA are mobilised from adipose tissue by alcohol, corticosteroids and in diabetics;
2. increased amount of FFA caused by increased synthesis or decreased degradation by oxidation in mitochondria;
3. decreased export of TG from hepatocytes. Failure of apoprotein synthesis leads to difficulty in export of TG as VLDL and hence FL [1]. This is an important pathogenic factor in the development of FL under influence of toxic substances (CCl_4, yellow phosphorus, etionine), some drugs (antibiotics, tetracyclines inhibiting protein production), low protein diet, exudative enteropathy or protein-caloric malnutrition

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Table 1. The aetiology of fatty liver.

1. Toxic factors:
• alcohol
• drugs (corticosteroids, methotrexate, 5-fluorouracyl, valproic acid, amiodarone, nifedipine, high doses of tetracyclines, oestrogens and vitamin A)
• toxic substance (CCl4 and the chloral carbohydrates, yellow phosphorus, amanityne, cocaine)
2. Nutritional factors:
• obesity
• bad eating (over-eating or protein-caloric malnutrition, kwashiorkor, diet with improper proportion of aminoacids choline and methionine)
• pancreatic disease
• total parenteral nutrition (TPN)
• jenuno-ileal bypass
3. Endocrine factors and metabolic diseases:
• diabetes mellitus
• primary and secondary hyperlipidaemias
• acute fatty liver of pregnancy
• early stages of Wilson's disease and hemochromatosis
• abetalipoproteinaemia, glycogenoses, galactosaemia, cholesterol esters storage disease, genetic defects of mitochondrial fatty acids oxidation
4. Other rare causes:
• chronic inflammatory bowel disease
• exudative enteropathy
• Reye's syndrome

(kwashiorkor; [1–3,5]). In some patients with FL, genetically dependent increased synthesis of apoB-MRNA was shown, which decreases production of apoprotein B in hepatocytes [6];

4. increased flow of carbohydrates into the liver, which are metabolised to the FFA (e.g. in diabetes mellitus; [1–5]).

The role of hepatic lipocytes, called Ito cells, in accumulation of lipids in the liver is still not fully established. The multiplication and enlargement of these cells are observed under influence of glycocorticosteroids, alcohol and prolonged administration of low-magnesium diet [2].

Many drugs can cause FL. Hepatocellular injury is usually due to a toxic metabolite of the drug. This follows exhaustion of intracellular substances such as glutathione. The free radicals produced by oxidative reactions of cytochrome P450 bind to proteins and to unsaturated fatty acids of cell membrane. This results in lipid peroxidation and membrane damage. The final outcome is hepatocyte death related to failure to pump calcium from the cytosol and to depressed mitochondrial function. The greatest necrosis is observed in central areas of the liver acinus (so-called zone 3), where drug metabolising enzymes are found in the highest concentration and where the oxygen tension is lowest in sinusoidal blood [1]. Fatty change is also seen in hepatocytes but inflammatory reaction is slight [1].

The main etiologic factors causing FL are alcohol, obesity, diabetes mellitus and hyperlipoproteinaemias [7]. Chronic alcoholism is the main etiologic factor in FL in countries with large alcohol consumption, but a degree of the liver changes is proportional to the time and amount of drinking [1,4,8].

Ethanol oxidation takes place in the hepatocyte cytosol. The acetaldehyde produced may be injurious in mitochondria and cytosol, causing membrane damage and cell necrosis [1]. Alcohol causes accumulation of lipids in hepatocytes through many mechanisms. It is know as a pure hepatotoxin to the liver cell damaging mitochondria and leading to the absence of ergastoplasm and focal degradation of cytoplasm. Alcohol is a high caloric compound (so-called empty calories) with easy oxidation in the hepatocytes, where it exchanges the residual carbohydrates [8,9].

In chronic alcoholism, FL is developed as a consequence of increased production and decreased oxidation of FFA in hepatic mitochondria, as well as a result of peripheral lipolysis of adipose tissue and increased flow of FFA into the liver [1,4,9-11]. In alcoholic FL, decreased amount of glutation in hepatocytes is observed. It leads to disturbances in detoxification processes [11,12]. Some significance is also ascribed to the disturbances in nutrition of the alcoholics. Nutritional factors are important, because the consumption of a meal rich in energetic products (carbohydrates and fat) and without proper amount of protein, can be a cause of FL, even in non-drinkers [8,9].

The important role in the pathogenesis of FL, particularly caused by alcohol and drugs, is played by the direct hepatocellular necrosis by free radicals and lipid peroxidation products with subsequent membrane damage [1]. It was shown in experimental studies that alcohol induces lipid peroxidation as a result of increased acetaldehyde and free oxygen radicals production [1,2,11]. Lipid peroxidation causes oxidation of pyridine nucleotides, accumulation of calcium anions, disturbed of func-

tion of many reticulum endoplasmic enzymes, release of hydrolytic enzymes from lysosomes, diminution of cell membrane fluidity, and finally, the damage of the liver cells [2]. Studies in vivo and in vitro in isolated hepatocytes showed, that lipid peroxidation disturbs lipoprotein excretion mainly on the level of their liberation from Golgi apparatus and with other toxic factors it leads to hepatocytes damage and accumulation of lipids inside them [13]. Lipid peroxidation not only indicates the degree of the cell damage, but it may also play a role in pathogenesis of FL, fibrosis and liver cirrhosis, through the damage of cell membrane and increased collagen production [11].

In alcoholic FL, the fat accumulates in centrizonal and midzone of the liver acinus (zones 3 and 2) [1]. In the more severely affected, the fatty change is diffuse. The fat may be in macrovesicular (large droplet) form. Less often, it is in microvesicular (small droplet) form. Microvesicular fat represents mitochondrial damage and more active lipid synthesis by the hepatocyte [1].

In alcoholic FL large fat droplets appear in the hepatocytes, dislocate cell nucleus and enlarge liver acinus [1,9]. In chronic alcoholism we can distinguish not only FL but also other morphological changes of the liver: acute alcoholic hepatitis (steatohepatitis, i.e. FL with necrosis of hepatocytes, inflammatory inflitrations with neutrophils mainly, sclerosing hyaline necrosis with collagen deposition in the central area of acinus, Mallory`s hyaline, enlarged (giant) mitochondria and frequently cholestasis), liver fibrosis (particularly in the region of central vein) and liver cirrhosis [1,3,8,9,14].

The patients with alcoholic FL are usually asymptomatic, sometimes with pain in liver region, enlarged and smooth liver. Liver function tests may be normal or transaminases and alkaline phosphatase are increased [1,3,4,15]

Alcoholic FL stops usually in the course of 4-8 weeks after discontinuation of drinking and the treatment is not necessary [3,4]. Until now, this disease was recognised as a mild pathology with a slight risk of the development of liver cirrhosis. Numerous observations of persons who continue drinking alcohol lead to the opinion that there is a risk of liver changes progression and possible development of liver cirrhosis in 10% of cases and liver fibrosis in 8% of cases after 10 years [16]. According to Teli et al, there are the indices of the histological progression of the liver damage like mixed small and large droplets fatty infiltrations and the presence of large mitochondria [16].

Obesity is the main non-alcoholic cause of FL [1,4,5,9,10,17]. The degree of steatosis correlates with the increase in body weight in both adults and children [1]. It is showed in increased lipolysis from the well developed adipose tissue and more FFA are supplied to the liver. This leads to an imbalance between TG synthesis and their secretion from the liver. There is also an imbalance between protein and calorie intake [1].

The study on the large number of obese persons showed the presence of FL in 91% of cases and steatohepatitis in 14% of cases [5]. Japanese studies on the large population of middle-aged people showed with the help of ultrasound (USG) that FL accompanies obesity in 18–24% of cases [18]. Body mass index, liver enzymes, TG, cholesterol and glucose in blood serum were higher in men with FL then in persons without FL. FL usually stops after administration of low-calorie diet and reduction of body mass [1,4].

The frequent cause of FL, particularly in obese person, are disturbances of lipid metabolism [1]. Retrospective analysis of patients with this changes and histologically confirmed liver damage showed different degree of hepatic injury from simple FL, FL with hepatitis (steatohepatitis) and FL with liver fibrosis or cirrhosis [19,20]. In patients with steatosis affecting over 60% hepatocytes, the TG serum level was double when compared with the group with less accumulated fat. In patients with steatohepatitis, TG level was twice higher than in patients with FL and liver fibrosis; these patients also had a significantly lower level of HDL [19,20].

The study on the correlation between FL diagnosed by USG and the disturbances in lipid metabolism in obese people showed the presence of FL in 17% of cases with hypercholesterolaemia and in 50% of cases with mixed hyperlipidaemias (total cholesterol was over 200 mg% and TG over 2, 3 mmol/l). The patients with mixed hyperlipidaemia and FL had TG twice higher and HDL lower in comparison to patients without FL [19,20].

Type 2 diabetes mellitus, particularly in obese and improperly treated subjects, is a common cause of FL [1,4,7,10]. Diabetes is marked by insulin deficiency and glucagon excess. This enhances lipolysis and inhibits glucose uptake thus increasing TG for-

mation by adipose tissue [1]. There are noticed disturbances of FFA metabolism in the liver and increased their release from the adipose tissue in diabetics [1,4,10]. Changes in oxidative phosphorylation in mitochondria, glucose metabolism with subsequent decrease of ATP level in hepatocytes, and disturbed binding of TG with apoproteins and their excretion from the liver are also seen in diabetics [5,21].

FL can develop in about 25-100% of patients given long term total parenteral nutrition (TPN). The increased transaminases, alkaline phosphatase and bilirubin values in blood serum (following approximately 2 weeks of treatment) are the main symptoms of FL in these cases [3,9,22]. Hepatic fatty change occurs partially with high glucose or other carbohydrates feeding when the rate of infusion exceeds the hepatic oxidative capacity so that fat is synthesised [1]. Choline deficiency plays a partial role in FL development [23,24]. It is recommended to maintain appropriate balance of TPN and choline or lecithin supplementation. FL is completely reversible, however the continuation of improperly prepared TPN can lead to the development of more pronounced hepatic lesions (e.g. steatohepatitis) [22,24].

Acute FL of pregnancy is a very severe disease and appears in every 6-13 thousands of pregnancies [1,3,9,25,26]. Its pathogenesis is not completely known. According to Sherlock, this disease belongs to the so-called mitochondrial cyto-pathies, which include Rey'e syndrome, some genetic defects, and rug caused dysfunction of these organelles [1]. In acute FL of pregnancy, there is inhibition of FFA beta-oxidation in hepatocytes mitochondria [1,3]. In most cases, nausea, vomiting, abdominal pain or jaundice appear during the third trimester of pregnancy. Biochemical tests show increased bilirubin and transaminases, prolonged prothrombin time and frequently, the syndrome of disseminated intravascular coagulation [3,4,26]. The diagnosis is based on the liver biopsy, which shows small droplet FL, necrosis of hepatocytes and deposits of fibrin in sinusoids [1,3,4,25]. The disease resolves usually after the delivery, therefore, the induction of delivery is the first-choice treatment; liver transplantation is rarely necessary [1,3,26].

Improper alimentation is another cause of FL. This disease is frequently seen in children with chronic protein-low alimentation in some tropical countries, in Africa, Asia and South America [1,4]. The liver changes in kwashiorkor are accompanied by other symptoms, like starvation anasarca or disturbances in consciousness [1,4,7,27]. FL in these cases resolves rather slowly as a result of diet rich in protein [27].

The diet short of choline can also cause FL [23]. Choline is necessary in phosopholipids production, which are the components of cellular membranes; it also participates in acetylcholine biosynthesis and is the source of methyl groups in the organism [23,24]. Lack of choline disturbs synthesis of phosphatydylcholine which is necessary in the secretion of VLDL from the liver [24].

Not fully explained role in the development of FL in some diseases (Reye's syndrome, lipid store diseases) is played by the disturbances of intracellular transport of FFA, caused by increased amount of fatty acid binding protein [14].

Morphology. FL is a histopathological entity. Increased accumulation of fat in the liver is divided into two morphological categories: macroscopic (large droplet, macrovesicular) and microscopic (small droplet; microvesicular) [1,3,4,15,25,28].

In macrovesicular FL, the hepatocytes are with punched out, empty vacuoles, and with the nucleus displaced to the periphery of the cell [1]. These changes are caused by the accumulation of fat containing vacuoles in the cell. It may be mostly found in alcohol, type II diabetes mellitus, obesity, protein calorie malnutrition, treatment with corticosteroids, high dose oestrogens, TPN, amiodarone, methotrexate and other toxic states (Table 1; [1,3,4]). These changes are frequently reversible, but only when etiologic factor is no longer active.

In microvesicular FL, small lipid droplets are presented in hepatocytes cytoplasm and mostly they do not dislocate the nucleus. Cell necrosis is variable and inconsiderable, there may occasionally be massive necrosis particularly in central area of acinus (zone 3) [1]. Histological examination of the liver shows hepatocytes with foamy cytoplasm and central nucleus [1,25,28]. The microvesicular FL can be related to a widespread hepatic metabolic disturbance, particularly involving mitochondria [1]. The most frequent causes are acute FL of pregnancy, Reye`s syndrome, hepatotoxic drugs (sodium valproate, large doses of tetracyclines), as well as less frequently alcohol and genetic defects of mitochondrial FFA beta-oxidation [1,4,25,28]. The onset of these diseases varies and in most instances, it remains obscure. Microvesicular FL is

frequently responsible for severe hepatic failure and multiorgan complications [1].

If we consider as a basis of histological analysis of the liver acinus, as the smallest functional part of the liver according to Rappaport, the lipid droplets can accumulate in periportal areas (zone 1), in acinar centre adjacent to terminal hepatic vein (zone 3) or in the whole acinus [1]. Steatosis is present most frequently in the middle of acinus, in zone 3, which is the microcirculatory periphery susceptible to many noxious factors [1,3,25,27].

FL may be either diffuse or focal. In the majority of clinical cases, diffuse FL is observed. Focal FL is recognised with USG, when areas of increased echogenicity, mostly located under the Glisson`s capsule, are seen in approx. 9–22% of cases [1]. It should be distinguished from other focal changes of the liver by the thin-needle aspiration biopsy under USG or CT guidance. The focal fat lesions are usually multiple and resolve with time, they may be seen in diabetics, alcoholics, the obese persons, those on TPN and with Cushing's syndrome [1,15].

The histological changes of the liver in patients with FL may be accompanied by inflammatory infiltrations (steatohepatitis), fibrosis or cirrhosis [1,3,4,9]. On the basis of aetiology, steatohepatitis may be alcoholic or non-alcoholic, and the histology of the liver may be similar in both groups with large or small droplets steatosis, inflammation, necrosis of hepatocytes, Mallory bodies, fibrosis [29–31].

Non-alcoholic steatohepatitis (NASH) is observed mainly in obesity (18% of cases according. to autopsy studies), several times more frequently in middle-age women with diabetes mellitus and hyperlipidaemia, moreover — in patients with thyroid insufficiency, jejuno-ileal bypass operations in obesity, in drug toxicity (e.g. amiodarone), TPN [1,13,17,29–31]. The aetiology of NASH is obscure. The great importance is associated with the hepatic damage related to lipid peroxidation due to oxidisable fat [5,13]. Moreover, the release of cytokines in NASH causes accumulation of FFA in the liver and the development of inflammatory and necrotic changes [13]. Symptoms of NASH are minor or absent. Occasionally, there is hepatomegaly, increased activity of transaminase, alkaline phosphatase, gamma glutamyl transpeptidase, serum transferrin saturation and ferritin [1,31]. Diagnosis of NASH is established with the liver biopsy when investigating a patient with elevated transaminases [29,30]. Histological examination shows macrovesicular or microvesicular FL and inflammation; Mallory bodies, fibrosis and cirrhosis may be present [1]. The treatment is unknown. The beneficial effect is obtained by body weight reduction, the attempts of the administration of ursodeoxycholic acid [29]. NASH frequently remains not diagnosed, lasting for a long time. This entity should always be considered in the individual with otherwise unexplained raised transaminases, whether or not they are diabetic or obese. It may be a cause of so-called cryptogenic liver cirrhosis diagnosed after several years of asymptomatic course [1,29–31].

Symptoms, clinical course and diagnosis. There is no difference between alcoholic and non-alcoholic FL in terms of the clinical picture, biochemical tests and histopathology of the liver [1,3,4,7]. Symptomatology and the clinical course of FL depend on the severity of degenerative changes in the liver, time-course of the etiologic factor affecting the liver and possibility of its elimination.

Clinical features are not characteristic. The patient is usually free of symptoms, may complain of right upper quadrant discomfort or heaviness, sometimes have nausea or vomits, and in more severe cases the deterioration of the general status with the signs of hepatic failure is observed. Examination of the patients shows usually the liver smoothly enlarged with soft consistency and occasional tenderness [1,3,4].

Uncomplicated and short lasting FL, e.g. after short-term alcohol abuse or after ingestion of drugs, is usually asymptomatic and without any important changes in biochemical tests. FL lasting for a long time (e.g. in obesity or diabetes mellitus) causes slight enlargement of the liver, meteorism, pain of the abdomen [1,3,4,7].

Severe dysfunction of the liver either from the normal status (e.g. in acute FL of pregnancy or after hepatotoxic drugs), as well as in deterioration of the already existing FL (e.g. acute viral infection in the patient with diabetes or in alcohol drinkers), may be presented with pain in the right upper quadrant, jaundice, increased cholestitic enzymes (alkaline phosphatase, gamma glutamyl transpeptidase) and transaminases, disturbances of the prothrombin time, finally with the clinical symptoms of hepatic failure [1,4,7].

Diagnosis of the FL is based on history, physical examination and additional studies including bio-

chemical tests, liver presentation in USG or CT, and histological examination of the liver biopsy, which is the most important diagnostic tool [3,15,19,20,27,31,32]. Biochemical tests poorly correlate with hepatic histology. Gamma glutamyl transpeptidase is usually elevated, serum transaminases and alkaline phosphatase are usually normal or slightly increased. FL is one of the most common causes of a raised serum transaminases activity detected in so-called 'healthy blood donors' [1].

Careful analysis of the anamnesis in necessary. The data concerning dietary habits, method of nutrition, alcohol abuse, accompanying chronic diseases, chronic abuse of drugs, metabolic and endocrine disturbances (e.g. diabetes mellitus, thyroid diseases), malabsorption syndromes or degree of circular and renal insufficiency are particularly important [3,4,15].

FL may be suspected in patients with chronic alcoholism, poorly controlled diabetes, obesity, hyperlipidaemia or malnutrition, in which the physical examination shows enlarged liver or on the basis of chronically observed slightly increased biochemical tests assessing liver function [15,32–35]. However, abnormal biochemical tests are seen only in approx. 30–40% of cases with FL [15].

Diagnosis of FL may be frequently confirmed by USG examination. Ultrasound may show bright echo pattern of the enlarged liver, but can be normal as well. Spleen and portal vein system are also normal [15,18,27,32,34]. In difficult cases, CT may be performed and show a reduced attenuation, which is less than that of the spleen or kidneys [1]. Magnetic resonance scanning is recently recommended. It may detect fat infiltrations and allows to assess it quantitatively [15,34,36]. The liver biopsy is the best method of diagnosis [1,3,4]. It is particularly useful when additional factors worsen the prognosis of FL (cardiac failure, viral infection, chronic treatment with drugs) or both clinical signs and biochemical tests suggests possible activation of inflammatory changes or development of the liver cirrhosis.

Treatment. FL is potentially reversible and in the majority of cases does not progress and does not lead to the liver cirrhosis. The prognosis, however, is bad in chronic alcoholics who continue drinking as well as in acute toxic FL [7,14,15].

The main principle of FL treatment is based on the elimination or minimisation of the etiologic factor or the introduction of appropriate therapy of the disease which caused FL. The following measures are recommended: reasonable balanced diet in obesity and in hyperlipidaemias, the discontinuation of alcohol drinking and ingestion of hepatotoxic drugs, proper dosage of insulin in diabetes mellitus, balanced composition of TPN [1,3,4,8,37]. Important elements of the FL therapy include the dietetic treatment and chronic use of pharmacological drugs properly selected against the particular etiologic factor [37].

The diet in FL should be individually selected for the patient, it should contain limited amount of high-calorie and saturated lipids substances, the optimal quantity of proteins, vitamins, particularly from group B [3,4,38]. The supply of all necessary aminoacids, including choline and methionine is very important, too [23,24]. It was shown, that both these aminoacids affect the metabolism of membrane phospholipids and increase the export of VLDL from the hepatocytes [23,24].

Some authors recommend the diet containing saturated fatty acids (e.g. palm oil) in alcoholic FL [37]. It was observed that theses acids, through down-regulation mechanism, decrease lipid peroxidation in hepatocytes, which plays an important role in the pathogenesis of alcoholic liver damage [2,37].

The pharmacotherapy with the so-called hepatotropic drugs or drugs which improve liver metabolism, is still controversial. Some authors recommend therapy with 'essential phospholipids' (EPL; [38,39]). Phospholipids are integral part of cell membrane and play an important role in the metabolism and oxidative processes [40]. During the damage of hepatocytes, the damage of the membranes takes place with release of phospholipids [39,40]. Administration of the exogenous EPL leads to the regeneration of membrane structure, improving the metabolic function of the hepatocytes [39,40]. Some clinical studies showed significant decrease of hepatic steatosis and the normalisation of the abnormal biochemical tests in patients treated with EPL. It is believed that protective of EPL on the hepatocyte membrane is based on the decrease of lipid peroxidation, improvement of membrane enzyme activity, diminution of steatosis and necrotic lesions of hepatocytes and the improvement of cell regeneration [40].

There are attempts to introduce the treatment of FL with glutation based on the fact that it decreases glutation concentration in hepatocytes, and it is

responsible for the dysfunction in hepatic detoxification processes [12]. Dentico et al. showed that glutation administered in large quantities in FL improved biochemical tests assessing the liver damage [12].

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